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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/701,013	01/12/2001	Masaaki Terada	0020.4769P	4777

2292 7590 03/14/2003

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/14/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/701,013	Terada et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Jan 23, 2003*.

2a) X This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *30-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *30-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) X The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) X Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) X All b) ☐ Some* c) ☐ None of:

1. X Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1	X Notice of References Cited (PTO-892)	4	☐ Interview Summary (PTO-413) Paper No(s).
2	☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5	☐ Notice of Informal Patent Application (PTO-152)
3	X Information Disclosure Statement(s) (PTO-1449) Paper No(s). 12	6	☐ Other:

DETAILED ACTION

Applicants' amendment filed 1-23-03 has been entered. Claims 1-29 have been canceled. Claims 30-36 have been added. Claims 30-36 are pending and under consideration.

Specification

1. The disclosure is objected to because of the following informalities: the abstract should only have one paragraph instead of two paragraphs.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 30-33, 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' amendment filed 1-23-03 necessitates this new ground of rejection.

Claims 30-33, 35 and 36 read on a stable gene formulation comprising an atelocollagen, a closed circular plasmid vector, and an ingredient, such as arginine, lysin, aspartic acid etc. (claims 30-33), or a citric acid or tartaric acid or a mixture thereof (claims 35 and 36).

The phrase "A stable gene formulation...comprising a) an **atelocollagen**; b) a closed circular plasmid..." in claims 30-33 and the phrase "A stable gene formulation...comprising a) a closed circular plasmid...further comprising an **atelocollagen**" in claims 35 and 36 are considered new matter. The specification fails to provide sufficient description for a stable gene formulation comprising an atelocollagen and a closed circular plasmid etc. No where in the specification discloses a gene formulation comprising an atelocollagen.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szoka et al., 1996 (WO 96/40265) in view of Fujioka et al., 1993 (US Patent No. 5,236,704) and Bonadio et al., 1998 (US Patent 5,763,416 A). Applicants' amendment filed 1-23-03 necessitates this new ground of rejection.

Claims 30-33 are directed to a stable gene formulation lyophilized from an aqueous solution comprising an atelocollagen, a closed circular plasmid vector containing a desired gene, and an ingredient, such as arginine, lysine, aspartic acid, glutamine, lactose, glucose, sorbitol etc. Claim 32 specifies the formulation further comprises a cationic lipid, a cationic polymer, or a hydrophobic polymer. Claim 33 specifies the formulation is in a rod form.

Szoka teaches polynucleotide complexes stabilized by adding a cryoprotectant compound, such as carbohydrate including lactose at a concentration of about 1.25% to 10% w/v, sucrose, glucose, mannitol, sorbitol, trehalose. The polynucleotide complexes could be plasmid DNA, polynucleoteide associated with a cationic lipid, or a polynucleotide associated with a liposome or lipidic particle. Szoka also teaches further adding amino acid, such as betaines prolines, polylysine, to stabilize the polynucleotide complexes (e.g. abstract, p. 2, 22). Szoka teaches lyophilization of the polynucleotide complexes and the lyophilized formulation may be stored for extended period of time and then rehydrate prior to use for gene delivery (e.g. abstract, p. 1, 24).

Szoka does not teaches using atelocollagen for gene formulation and preparing the formulation in a rod form.

Fujioka teaches preparation of a controlled release formulation by lyophilizing a mixture of an active ingredient such as protein or peptide, collagen such as **atelocollagen** and an appropriate amount of an acidic compound as an additive, pulverizing the resulting solid product, and compression-molding the pulverized product in a template or charging the above-mentioned mixture in a template and condensing or drying the mixture, so as to obtain the formulation in a solid form, whereby any formulation, having a desired size and shape suitable for a particular administration route and a particular position to be applied can be obtained. Specific examples for the shape of the formulation are listed as: bar-like, rod-like, needle-like, disk-like, film-like, and spherical shape (e.g. column 4 bridging column 5). The afore-mentioned mixture can also be blended and kneaded in the presence of an appropriate amount of water or buffer, and subjected to injection-molding followed by drying to prepare a needle-like or bar-like shaped formulation (e.g. column 1, 3, 4, 5, 10, 11). Fujioka teaches sustained release formulations, which release an active ingredient over a long period of time, are useful for the increase of therapeutical effects due to prolonged retention of an active ingredient over effective level in the blood, the decrease of side-effects by reducing the maximal blood level of the active ingredient, simplification of administration methods and a reduction in a patient's level of pain due to a decrease of administration frequency (e.g. column 1).

Bonadio teaches a composition comprising a nucleic acid segment in association with a structural bone-compatible matrix, wherein said **nucleic acid segment** is a DNA molecule, RNA molecule, or antisense nucleic acid molecule and said nucleic acid segment can be inserted within genomes of recombinant viruses, wherein said matrix is a **collagen preparation**, hydroxyapatite, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix (e.g. column 4, 5, 22, 66 and 68). Bonadio also teaches a method for transferring a nucleic acid segment into bone progenitor cells located within bone progenitor tissue comprising contacting said tissue with a composition comprising a nucleic acid and a structural bone-compatible matrix, such as a collagen preparation, wherein said nucleic acid expresses transcriptional or translational products in said cells (e.g. column 63-65).

It would have been obvious for one of ordinary skill at the time of the invention to use an atelocollagen for the preparation of a stable gene formulation because Bonadio teaches a composition comprising a **nucleic acid segment** in association with a structural bone-compatible matrix, such as a **collagen preparation** for transferring the nucleic acid segment into bone progenitor cells located within bone progenitor tissue and Fujioka teaches preparation of a controlled release formulation comprising an active ingredient, such as protein or peptide and a collagen, such as an **atelocollagen**, and said formulation can release the active ingredient over a long period of time for increased therapeutic effects of the active ingredient. It also would have been obvious for one of ordinary skill at the time of the invention to prepare a stable gene formulation comprising a closed circular plasmid DNA because it was well known in the art that

plasmid DNA has three different forms, i.e. closed circular (supercoiled DNA), relaxed, and linear DNAs, and a plasmid DNA preparation usually contains closed circular (supercoiled DNA) and relaxed DNAs. Therefore, the plasmid DNA taught by Szoka would comprise closed circular plasmid vector.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to generate a stable polynucleotide complex for gene transfer as taught by Szoka or to produce sustained release formulations which release an active ingredient over a long period of time and are useful for the increase of therapeutical effects due to prolonged retention of an active ingredient over effective level in the blood, the decrease of side-effects by reducing the maximal blood level of the active ingredient, simplification of administration methods and a reduction in a patient's level of pain due to a decrease of administration frequency as taught by Fujioka with reasonable expectation of success.

6. Claims 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujioka et al., 1993 (US Patent No. 5,236,704) in view of Bonadio et al., 1998 (US Patent 5,763,416 A) and Szoka et al., 1996 (WO 96/40265). Applicants' amendment filed 1-23-03 necessitates this new ground of rejection.

Claims 34-36 are directed to a stable gene formulation lyophilized from an aqueous solution comprising a closed circular plasmid vector containing a desired gene, and a citric acid, tartaric acid or a mixture thereof. Claim 35 specifies the formulation further comprises an

atelocollagen. Claim 36 specifies the formulation further comprises a cationic lipid, a cationic polymer, or a hydrophobic polymer.

Fujioka teaches preparation of a controlled release formulation by lyophilizing a mixture of an active ingredient such as protein or peptide, collagen such as atelocollagen and an appropriate amount of an acidic compound having one or more carboxylic groups, such as citric acid and tartaric acid, as an additive, pulverizing the resulting solid product, and compression-molding the pulverized product in a template or charging the above-mentioned mixture in a template and condensing or drying the mixture, so as to obtain the formulation in a solid form, whereby any formulation, having a desired size and shape suitable for a particular administration route and a particular position to be applied can be obtained. Fujioka also teaches preparation of an aqueous solution containing 2 w/w% atelocollagen, an acidic compound and a growth hormone releasing factor, wherein the aqueous solution is lyophilized to prepare a column-shaped formulation which is administered subcutaneously to rats (e.g. column 7, 8, 9). Fujioka teaches sustained release formulations, which release an active ingredient over a long period of time, are useful for the increase of therapeutical effects due to prolonged retention of an active ingredient over effective level in the blood, the decrease of side-effects by reducing the maximal blood level of the active ingredient, simplification of administration methods and a reduction in a patient's level of pain due to a decrease of administration frequency (e.g. column 1).

Fujioka does not teach gene delivery to the cells of a subject via a composition comprising a closed circular plasmid vector or the composition further comprises a cationic lipid.

Bonadio teaches a composition comprising a nucleic acid segment in association with a structural bone-compatible matrix, wherein said nucleic acid segment is a DNA molecule, RNA molecule, or antisense nucleic acid molecule and said nucleic acid segment can be inserted within genomes of recombinant viruses, wherein said matrix is a collagen preparation, hydroxyapatite, lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid polymer matrix (e.g. column 4, 5, 22, 66 and 68). Bonadio also teaches a method for transferring a nucleic acid segment into bone progenitor cells located within bone progenitor tissue comprising contacting said tissue with a composition comprising a nucleic acid and a structural bone-compatible matrix, such as a collagen preparation, wherein said nucleic acid expresses transcriptional or translational products in said cells (e.g. column 63-65).

Szoka teaches polynucleotide complexes stabilized by adding a cryoprotectant compound, such as carbohydrate including lactose, sucrose, glucose, mannitol, sorbitol, trehalose. The polynucleotide complexes could be plasmid DNA, polynucleoteide associated with a cationic lipid, or a polynucleotide associated with a liposome or lipidic particle. Szoka teaches lyophilization of the polynucleotide complexes and the lyophilized formulation may be stored for extended period of time and then rehydrate prior to use for gene delivery (e.g. abstract, p. 1, 24).

It would have been obvious for one of ordinary skill at the time of the invention to prepare a stable gene formulation comprising a closed circular plasmid DNA because it was well known in the art that plasmid DNA has three different forms, i.e. closed circular (supercoiled DNA), relaxed, and linear DNAs, and a plasmid DNA preparation usually contains closed

circular (supercoiled DNA) and relaxed DNAs. Therefore, the plasmid DNA taught by Szoka would comprise closed circular plasmid vector. It would have been obvious for one of ordinary skill in the art at the time the invention to substitute the growth hormone releasing factor in the atelocollagen preparation as taught by Fujioka with a closed circular plasmid vector and a cationic lipid as taught by Szoka because Bonadio teaches delivering a compositions comprising collagen and nucleic acids to cells and Szoka teaches polynucleotide complexes stabilized by adding a cryoprotectant compound and a cationic lipid or a liposome.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to stabilize a gene preparation as taught by Szoka or to deliver a closed circular plasmid vector containing a gene in a controlled release formulation which releases the vector over a long period of time for gene transfer to the cells of a subject as taught by Fujioka and Bonadio with reasonable expectation of success. The controlled release formulations have been recognized to be useful in various aspects: increase of therapeutical effect due to prolonged retention of an active ingredient over effective level in the blood, decrease of side-effects by reducing the maximal blood level of the active ingredient, and simplification of administration methods and reduction of patient's pain due to a decrease of administration frequency.

Applicants argue that Szoka does not describe atelocollagen as a component of the formulation and Fujioka does not describe a closed circular plasmid vector in the gene preparation. Applicants further argue that closed circular plasmid DNA is quite different from

peptide or protein as disclosed by Fujioka (amendment, p. 6-8). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 103(a) rejection.

Applicants argue that the present invention provides experimental results that are not expected by one of ordinary skill in the art (amendment, p. 8, 9). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 103(a) rejection and that the claimed invention are products comprising an atelocollagen, a closed circular plasmid vector, and/or an ingredient, and those products are obvious to one of ordinary skill at the time of the invention according to the collective teachings of Fujioka, Szoka and Bonadio as discussed above. The unexpected result disclosed in the specification is irrelevant to the claimed products.

Conclusion

No claim is allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MEP. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D. S. L. Chen